Aus der Abteilung für Experimentelle Anaesthesiologie
des Institutes für Anaesthesiologie
der Universität Düsseldorf
(Leiter: Prof. Dr. Joachim O. Arndt)

BLOOD VOLUME DISTRIBITION AND THE INTERACTION OF VASOACTIVE DRUGS DURING PERIDURAL ANAESTHESIA IN MAN

Dissertation

zur Erlangung des Grades eines Doktors der Medizin
der Medizinischen Fakultät der Universität Düsseldorf
vorgelegt von

Michael d'A. Stanton-Hicks

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Introduction

Major conduction anaesthesia is associated with a loss of vasomotor tone which is reflected for example, by a strong increase in blood flow in the denervated limbs (Rovenstein et al., 1942, Greene, 1969). Disturbance of the arterial side of the circulation i.e., a disturbance of the flow/resistance relationship is therefore presumed to be the main reason for the arterial hypotension that in combination with elevated cardiac output usually accompanies major conduction anaesthesia (Ward et al., 1965). In contrast to the numerous publications dealing with arterial hemodynamics, little is known about the response of the low pressure side of the circulation to the loss of vasomotor tone, a fact which is also likely to disturb the relationship between vascular capacity and blood volume, thereby jeopardizing cardiac filling (Guyton, 1956). Blood pooling in the denervated skeletal musculature which, as has been shown by plethysmography (de Marée et al., 1975), together with the fall in central venous pressure during major conduction nerve block (Kennedy et al., 1969) do in fact argue for a change in the blood volume distribution at the expense of cardiac filling. However, the extent of this effect is still in doubt. It was therefore one aim of the present experiments to see if and to what extent peridural anaesthesia would alter the distribution of blood volume in man, particularly with respect to cardiac filling using whole body scintillography (Höck et al., 1977).

A further aspect addressed the feasibility of how to counteract the PDA-induced cardiac filling disturbances with vasoactive drugs. Dihydroergotamine, an α-antagonist with venoconstrictur properties (Brügger, 1945, Mellander, Nordenfelt, 1970), and etilefrinehydrochloride, an α- and ß-agonist (Hengstmann et al., 1975, Müller et al., 1983) appeared to be promising choices. Both improve cardiac filling by mobilizing blood from different sources in healthy men with intact vascular innervation, dihydroergotamine by expelling blood preferentially from the skeletal musculature, etilefrine from the splanchnic circulation, and in combination both drugs increased cardiac volume and pressures in an additive fashion (Arndt et al., 1984).

A final aspect of this study relates to the peripheral blood flow during PDA and its response to dihydroergotamine and etilefrine. Dihydroergotamine increases resting blood flow in the skeletal musculature of man with intact vascular innervation but decreases it when blood flow is elevated as, for example, during spinal anaesthesia (Castenfors et al., 1975). Thus vasomotor tone would seem to play an important role in determining the action of these drugs. It was therefore of considerable interest to see how peripheral blood flow in the denervated limbs would respond to the combined action of dihydroergotamine and etilefrinehydrochloride.

The technique of scintilation counting of ^{99m}Tc-labelled erythrocytes to follow the changes in regional blood content under the conditions imposed by the proposed study protocol

seemed to provide both the accuracy and specificity required for an appropriate interpretation of blood volume distribution (Smith and Richards, 1976, Höck et al., 1977). Since this approach yields information only on the relative distribution of the blood throughout the circulatory system, we complemented this study by plethysmography of the lower limbs. In this way it was possible to quantitate both filling and blood flow in the lower limbs.

To reiterate, the present investigation was designed to address three main questions:

1. How does peridural anaesthesia to the fifth thoracic spinal segment affect the regional distribution of blood?
2. How does dihydroergotamine alone and in combination with etilefrine modify the regional blood distribution consequent upon peridural block?
3. How does dihydroergotamine alone and together with etilefrine affect blood flow in the denervated limbs?

PDA will be shown to redistribute blood into the denervated musculature at the expense of cardiac filling, an effect, that can be reversed by DHE which mobilizes blood from the musculature, and by E which preferentially expels blood from the splanchnic circulation in favour of the heart. Evidence will also be presented for the contention that the splanchnic vasculature plays a crucial role for cardiovascular stability during PDA.

2. Methods

Eight healthy, male volunteers (four physicians and four medical students) between the ages of 22 - 42 (average 33 years) with a body weight of 77kg (range 60-92) gave their informed consent to participate in the study. They had fasted overnight and were studied in the horizontal decubitus position at a room temperature of 27°C in the morning between 0900 and 1300 (six experiments) and in the afternoon between 1300 and 1700 (two experiments). No fluids were given intravenously. Immediately prior to each study, 5 ml of venous blood werewithdrawn for erythrocyte labelling with technicium (^{99m}Tc, 5 mCi=5x37MBq) and injected intravenously (Höck et al., 1977).

A peridural catheter was inserted through an 18 gauge Crawford needle at the L2-3 interspace. Both brachiocephalic veins were cannulated, one for drug infusion, the other for recording of central venous pressure (CVP) via a cathether advanced into the right atrium. Heart rate was derived with an ECG-triggered cardiotachometer and blood pressure sphygmomanometrically. Whitney strain gauges (Whitney, 1953) around both calves served to follow calf volume and to measure calf blood flow by occlusion plethysmography. The resting circumference was measured by tape initially and the strain gauge then calibrated at frequent intervals by an in-series micrometer. Finally, two blood pressure cuffs (width 20 cm) were loosely fixed around the thighs. When pressurized to 100 mmHg, blood

could be pooled in the lower limbs (leg congestion test).

The placement of the various catheters and transducers took about half an hour, an interval sufficient to allow for the equilibration of the labelled erythrocytes. After this period the actual experiments commenced.

The radioactivity was recorded continuously by whole body scintillography using a gamma camera (Searly LFOV, equipped with a parallel hole, high resolution collimator) in the anterior-posterior direction. The counting sequence employed in this instance commenced on the left side from foot to head, and in the reverse order on the right side. Each counting cycle occupied six minutes (= 1 scan) repeated without interruption over the duration of each study for a total of 96 minutes, i.e. 16 scans. The counts were acquired by a computer (DEC PDP 11/15), stored,processed, and whole body images reconstructed for each scan. Average counting rates (counts per scan = cps, corrected for the physical decay of ^{99m}Tc) were printed for the following regions:

1. skeletal muscle (legs and arms)
2. splanchnic region (abdomen and liver plus spleen)
3. thoracic region (lungs and heart).

Drugs used: Lidocaine (2% Xylocain^{R}) for PDA and the vasoconstrictor agents dihydroergotamine (DHE) and etilefrine-hydrochloride (E). DHE is an α-antagonist with venoconstrictor properties, whose vascular effect last for several hours after

intravenous injection (Mellander and Nordenfelt, 1970, Aellig and Nüest, 1977, Berde and Schild, 1978). E is a catecholamine with α- and some ß-agonist activity the cardiovascular effects of which last for 30 - 45 minutes after intravenous injection of the therapeutic dose (Mellander, 1966, Hengstmann et al., 1975, Inoue et al., 1979).

Experimental protocol:

All experiments commenced about one hour after the injection of the tracer. The following scheme was adopted in each subject:

1. Control I, 18 min (= scan 1 - 3)
2. Peridural anaesthesia, 24 min (= scan 4 - 7)
   Xylocain (20 ml) was injected at the start of scan 4 and the sensory block (tested by pin prick) to T4/5 was achieved within 18 min in each case.
   Dihydroergotamine (DHE), 18 min (= scans 8 - 10).
   DHE (7.5 µg/kg) was given over 5 min during scan 8, and the subsequent effects were monitored through scans 9 - 10.
3. Etilefrinehydrochloride (E) 18 min (= scans 11 - 13).
   E was infused (6 µg/kg/min) for 18 min.
4. Control II, 18 min (= scans 14 - 16) after discontinuation of the E-infusion.

Radioactivity, central venous pressure, heart rate and calf volume were recorded continuously throughout the experiment and systemic arterial pressure and calf blood flow were always measured at the end of each scan. Leg congestion tests were performed during scan 2 and 14.

Data analysis:

Data are expressed as averages (± SE). To demonstrate the time course of the effects of radioactivity in the various regions each is expressed as a percent of the third scan (= 100). A comparison between the maximum changes in radioactivity was used to show the differences in effects of the various manoeuvres. The Wilcoxon Rank test was employed for testing differences with p-values < 0.05 being considered significant.

3. Results

3.1 Blood distribution

As illustrated in fig. 1, PDA caused an increase of radioactivity only in the denervated legs. In all other regions, namely in the thorax, the innervated upper limbs and surprisingly, the abdomen, it decreased. These effects developed gradually in parallel with the ascent of the sensory block which reached its highest level between T4 and T5 within 18 min of the peridural injection of lidocaine and remained at this level for the following 40-45 min (until scan 14).

The leg congestion test carried out during scan 2 of the control period mimicked the effects of PDA with respect to the thoracic and abdominal region, and gave a rough indication of the extent to which PDA induced a redistribution of the blood volume as an amount of approximately 600 ml was pooled in both legs by this manoeuvre (see discussion).

DHE restored the PDA-induced effects. It strongly reduced the radioactivity in both the innervated arms and denervated legs in favour of the thorax and also the abdomen. In the legs, DHE not only reversed the PDA-induced effects, but it reduced the counting rates below the values which were present before the conduction block was induced.

DHE alone therefore displaced blood preferentially from skeletal musculature, both innervated and denervated, into the thoracic and splanchnic vasculature.

E acted most obviously in the splanchnic area, where the

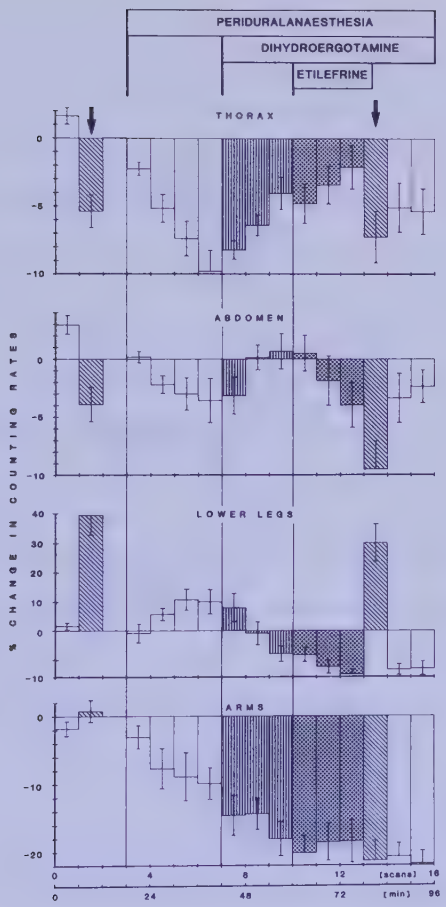

Figure 1: Changes of blood volume in the regions indicated are expressed as the percentage change in counting rates of radioactive ^{99m}Tc-labelled erythrocytes during peridural anaesthesia (PDA), dihydroergotamine (DHE) and etilefrinehydrochloride (E). Each sampling period, i.e., whole body scan = 6 min. Third scan is control (= 100). Leg congestion test performed during scans 2 and 14. Averages (± S.E.M.) n=8.
The reduction in counting rates under PDA is reversed by the influence of DHE and E. The effects of PDA are duplicated by leg congestion tests during scans 2 and 14.

radioactivity greatly decreased. The counting rate in the legs continued to fall during the infusion of E, but it appeared to have no effect on the arms. With E, the only increase in radioactivity was seen in the thorax. Following discontinuation of the E-infusion at the end of the experiment (see last two scans), a change in the thoracic and abdominal counting activity in the opposite direction was noted. This is a further indication that E had mobilized blood preferentially from the splanchnic vasculature in favour of the thoracic circulation. While it might be argued that because regression of the block to a sensory level of L2-3 had occurred by this time, the sympathetic block was still in all probability some 2-3 segments higher, in which case for the most part the leg vessels were still denervated.

To illustrate the response of special organs like the heart, liver and spleen to the various experimental manoeuvres, fig. 2, contrasts the maximum changes in counting rates which occurred in each of the measured regions. During PDA, the counting rates decreased in all regions except the lower limbs where significant increases were noted. In contrast, dihydroergotamine decreased the counting rates in the skeletal musculature and increased them in the thoracic and abdominal regions. E, however, lowered the counting activity in the splanchnic region and increased it in the thorax. Finally, the leg congestion test duplicated both qualitatively as well as quantitatively the effects of PDA.

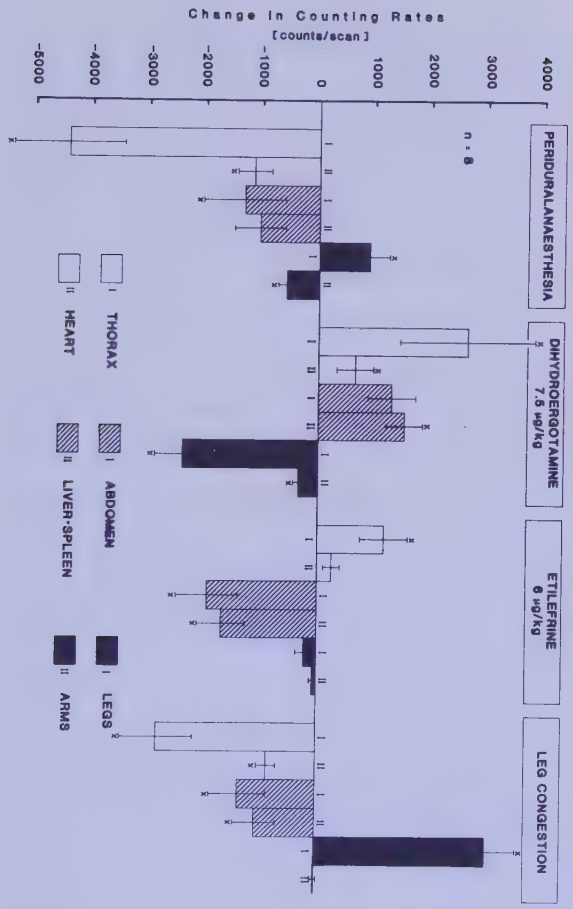

Figure 2: Changes in counting rates (cps = counts per scan) in each region during peridural anaesthesia (PDA), dihydroergotamine (DHE) and etilefrinehydrochloride (E). The maximum differences between the last scans of each period are shown, i.e., PDA-control, DHE-PDA, E-DHE, Leg congestion-E. Averages (± S.E.M.) n=8. Wilcoxon Rank Test. x=P $<$ 0.05.
PDA caused an increase in counting activity in the legs, in all other regions it decreased. Leg congestion mimicked the effects of PDA. DHE reversed the effects of PDA, increasing the counting activity in the abdomen, while E had a selective action in the abdomen further enhancing the counting activity in the thorax.

In the abdomen and partially also the thorax the actual changes in counting rates are to some degree affected by the response of the striated musculature in these regions. This would tend to underestimate the effects of the PDA and also of DHE, less so that of E which has minimal effects on the skeletal muscle vessels. But the contribution of the vessel-rich organs like the liver and spleen to the overall activity appears to predominate by far as the changes in counting rates are almost the same for the restricted liver/spleen region and total abdomen.
Thus PDA redistributes blood mainly into denervated muscle regions at the expense of cardiac filling which is normally associated with a decrease in blood content in the innervated musculature and the splanchnic circulation, too. These effects are reversed by DHE and E, the former mobilizing blood preferentially from the skeletal musculature, while the latter has an action mainly on the splanchnic vessels, the combined effects of which favour filling of the thoracic circulation.
The splanchnic vasculature needs a special note because its response seems to be linked with cardiovascular stability during PDA. This is apparent from tab. 1 which lists the percent changes in counting rates for each subject. It documents the uniform effects of PDA in the thorax and muscle regions. Without exception counting rates decreased in the thorax and innervated arms but they increased

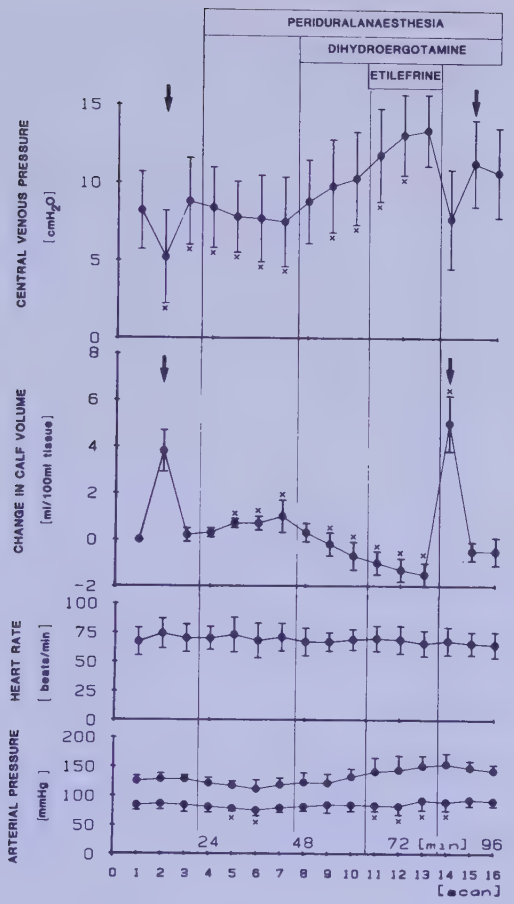

Figure 3: Central venous pressure (CVP), calf volume, heart rate and arterial pressure during peridural anaesthesia (PDA) dihydroergotamine (DHE) and etilefrinehydrochloride (E). Averages (± S.E.M.) n=8. Wilcoxon Rank Test. x=P $\leq$ 0.05.
The slight fall in CVP which occurred during PDA is more than reversed by the combined effects of DHE and E. Calf volume can be seen to reflect the changes of CVP in an opposite sense. Heart rate is unchanged and the arterial pressure reflects the influence of DHE and E by an increase of pulse pressure.

Regional counts in percent of scan 3 (= 100) before (control) and during peridural anaesthesia (peridural). The arabic numbers designate the number of scans with each scan lasting 6 min. Lidocaine (20 ml 2%) was injected intraperidurally at the end of scan 3 and a leg congestion test performed during scan 2.

Region	Subject	Control			Peridural $T_{4/5}$			
		1	2	3	4	5	6	7
Thorax	1	1.7	-10.1	100	- 0.4	- 2.4	- 4.7	- 9.0
	2	2.2	- 1.7	100	- 1.2	- 2.0	- 4.0	- 3.8
	3	0.4	- 5.0	100	- 4.0	- 7.2	- 9.1	-10.4
	4	2.0	- 6.6	100	- 3.0	- 8.2	-13.3	-12.9
	5	5.0	- 7.2	100	- 1.3	- 3.9	- 4.0	- 5.0
	6	±0	- 4.3	100	- 3.3	- 9.7	-11.3	-11.3
	7	-0.3	- 5.0	100	- 3.6	- 5.1	- 7.9	- 7.6
	8	1.9	- 9.0	100	- 1.2	- 2.7	- 4.5	- 4.5
Abdomen	1	1.2	-12.3	100	- 2.4	- 2.2	-12.4	-12.2
	2	3.9	- 2.3	100	- 1.6	- 2.9	- 4.3	- 5.7
	3	5.8	- 2.5	100	- 1.4	- 7.4	- 7.5	-12.5
	4	3.1	- 4.5	100	- 0.4	- 7.6	- 1.2	- 2.4
	5	4.6	+ 0.7	100	± 0	- 3.3	- 4.3	- 4.7
	6	±0	- 2.9	100	± 0	- 6.3	+ 0.4	+ 0.4
	7	-3.7	- 2.5	100	± 2.8	- 2.8	- 3.9	- 1.3
	8	-4.5	- 8.0	100	- 3.4	- 0.3	- 1.6	- 1.6
Lower legs	1	+3.5	+21	100	± 0	+ 3.0	+ 4.4	+ 4.4
	2	-3.6	+60	100	± 6.0	+ 9.2	+12.3	+ 3.3
	3	+6.9	+45	100	+16.8	+13.2	+32.2	+36.1
	4	+2.9	+55	100	+ 3.0	+12.9	+16.0	+16.4
	5	+0.1	+20	100	- 3.7	+ 1.6	+ 3.7	+ 4.0
	6	-1.0	+37	100	+ 4.0	+ 6.0	+ 4.4	+ 4.4
	7	-0.8	+15	100	- 4.3	- 0.1	+ 4.2	+ 5.7
	8	+4.5	+64	100	- 2.6	+ 4.6	+10.9	+10.5
Arms	1	-2.0	+ 6	100	- 1.1	+ 6.1	+ 7.7	- 0.5
	2	-1.7	+ 8.1	100	- 6.6	- 0.5	- 6.2	- 2.1
	3	+2.6	+ 0.2	100	- 1.3	- 4.9	- 0.9	-12.8
	4	±0	- 2.4	100	- 9.5	-22.2	-23.8	- 7.3
	5	-1.2	- 0.4	100	- 4.8	- 8.0	- 7.0	-11.5
	6	±0	- 1.3	100	- 4.9	-11.5	- 9.3	- 9.3
	7	-5.2	- 5.9	100	- 3.1	- 8.9	-12.4	-16.7
	8	-6.8	- 1.9	100	- 6.6	-11.7	-19.2	-19.1

in the denervated limbs. However, the response of the splanchnic region is less uniform. Here, the activity decreased after an early fall in six, but increased in two of the subjects (No.4 and 5) during PDA. This is particularly noteworthy because in subjects 4 and 6, thoracic counting rates, arterial pressure though not central venous pressure, exhibited the greatest falls. In fact, vasovagal syncope (heart rate dropped from 65 to 48 beats/min and blood pressure from 130/100 to 90/50 mmHg in combination with sweating and dizziness) occurred in subject 4.

3.2 Pressures, heart rate and calf volume

Central venous pressure clearly mirrored the described changes in blood content within the thoracic region. This is evident from fig. 3. A slight fall in the central venous pressure of 1.25 cm water occurred in all cases during the development of the nerve block. This fall can be contrasted with the increase of 6 cm water which resulted from the combined actions of DHE and E respectively. These effects are clearly additive. As evidence of the short lived action of E, CVP rapidly decayed and reached the previous level which had been established by DHE alone within 12-18 min (scan 15 and 16) following its discontinuation.

The exaggerated fall of the CVP during leg congestion at the end of the experiments, i.e. (scan 14), can be explained by the rapid decay of the E-induced central venous pressure rise. If the results of both leg congestion tests are com-

pared, namely scan 2 and 14, one sees a reversal of the pressure changes which upon release of the occlusion cuffs, i.e. during scans 3 and 15, the effects for the most part being equivalent to a difference in pressure of about 3.5 cm water.

Calf volume mirrored the changes in central venous pressure. It increased by about 1 ml/100 ml tissue during PDA but decreased by 1.67 ml/100 ml tissue after the injection of DHE and by a further 0.83 ml/100 ml tissue during the infusion of E. The combined action of both agents therefore mobilized a total of 2.5 ml blood per 100 ml muscle tissue. DHE which in isolation constricts blood vessels in the skeletal musculature of both the denervated and innervated regions therefore expelled about 500 ml of blood if the muscle mass is assumed to represent about 40 percent of the body weight.

During leg congestion, the calf volume increased significantly by 4 ml/100 ml tissue. If the leg is regarded as a cylinder, roughly 60 cm in length having a circumference, corresponding to that of the calf of 38 cm, one can calculate an uptake of about 600 of blood within both legs. This estimate supports the contention that the changes in central venous pressure with the various manoeuvres described above are to a large extent determined by the shifts in blood volume between the intrathoracic and muscle vessels.

The heart rate changed little on average and arterial pressure paralleled CVP. During PDA, systolic, diastolic and pulse

pressure decreased, while all pressure components increased under the influence of DHE and E. E in particular elevated systolic pressure and thereby pulse pressure as is evidenced by the disappearance of these effects in the post-infusion period.

Although the average fall in blood pressure during PDA is but small for this group of subjects the individual responses were quite different. This is obvious from tab. 2. Blood pressure remained constant or even increased in most subjects but fell most markedly in two (subject 4 and 6) of which one actually fainted (subject 4) as mentioned above.

3.3 Blood flow in the lower limbs

Peridural anaesthesia is known to increase blood flow in the denervated regions. As seen in fig. 4, PDA almost doubled the calf blood flow, but most importantly, this flow remained elevated, even after the injection of DHE. This clearly demonstrates that DHE, while maintaining the venoconstrictor effect, did not have an action on the resistance vessels during PDA.

The action of E on the blood flow in the denervated leg is less clear. Calf blood flow decreased during the infusion of E but this effect was not reversed during the post-infusion period. Instead, there was a further decline towards the control level. This effect, as already mentioned, may be a reflection of returning sympathetic function in the lower limbs. Nevertheless, it is important to note that blood flow

Tab. 2 Changes in mean arterial blood pressure mmHg before (control) and during peridural anaesthesia (peridural). The arabic numbers designate the number of scans with each lasting 6 min. Lidocaine (20 ml 2%) was injected at the end of scan 3 and the leg congestion test performed during scan 3. Arterial pressure was measured at the end of each scan and the changes are referred to scan 3.

	Control			Peridural $T_{4/5}$			
Subject	1	2	3	4	5	6	7
1	+5	+ 7	93	± 0	- 5	- 5	± 0
2	+2	+13	90	+ 7	+ 7	+ 7	+ 3
3	-3	+ 7	103	+ 7	-18	- 8	± 0
4	±0	± 0	110	-13	-17	-57	-23
5	±0	± 0	93	- 1	± 0	- 3	- 3
6	±1	- 9	107	-17	-14	-20	-20
7	±3	± 3	87	± 0	- 9	± 0	± 0
8	±2	± 3	90	± 0	± 0	± 0	- 2

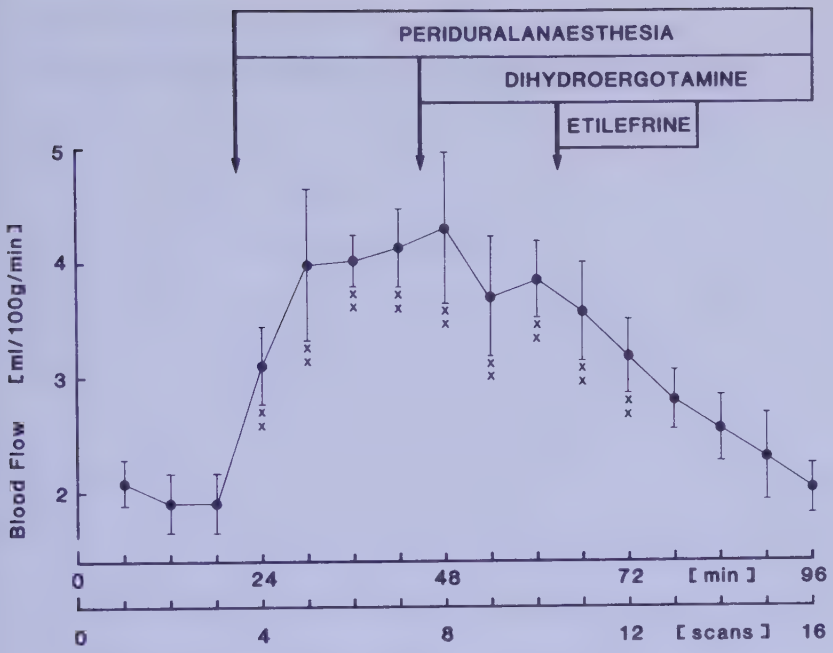

Figure 4: The influence of peridural anaesthesia (PDA), dihydroergotamine (DHE) and etilefrinehydrochloride (E) on calf blood flow. Averages (± S.E.M.) n=6. Wilcoxon Rank Test. x=P $\leq$ 0.05.
The strongly increased blood flow during PDA is not affected by DHE and remains even during the combined action of DHE and E well above the values before PDA was induced.

during the maximum effect of E is still well above the values which were measured before PDA and again at the end of the recording period.

4. Discussion

4.1 General aspects of the cardiovascular actions of PDA

Peridural anaesthesia can influence the cardiovascular system in two ways; by blocking sympathetic neural drive and/or by direct effects of the absorbed local anaesthetic on the heart and/or vascular smooth muscle.

Like spinal anaesthesia, peridural anaesthesia induces a preganglionic sympathetic block, the magnitude of effects being determined by the number of affected spinal segments. With block of the lower thoracic and lumber segments it is generally accepted that the effects are limited to "pooling" of blood in the so-called "dependent" or denervated areas (de Marées et al., 1975). If the block exceeds the 9th thoracic segment, the neural drive to the adrenal medulla is interrupted (Cousins, 1980). Block of the upper five thoracic segments prevents the normal sympathetic control to the heart with the result that there is a loss of both chronotropic and inotropic influences on the myocardium (Otton and Wilson, 1966, Cousins, 1980, Malliani, 1972).

The direct effects of local anaesthetics depend upon plasma concentration: at low levels mild cardiac stimulation ensues but with high blood levels, negative inotropic effects are seen on the myocardium and the vascular smooth muscle is relaxed (Jorfeldt et al., 1968, Tucker and Mather, 1975).

In the present study, a dose of lidocaine (400 mg), i.e. 20 ml of 2 % solution without vasoconstrictor was chosen

to achieve a segmental block to a level of T4/5 and a sympathetic block some 2 to 3 segments higher. The systemic blood level expected from this dose should have been no higher than about 3 µg/ml, in which case no depressant effects should be expected (Tucker and Mather, 1975), and only the loss of neural and adrenal influences on the circulation, in particular the low pressure system need therefore to be considered here.

4.2 Physiology of the low pressure system

In order to interpret the foregoing observations, particularly with regard to their extent and possible functional significance, it is important to consider some of the characteristics relating to the low pressure side of the circulation. Three aspects are relevant to the data presented: the response of the central venous pressure to induced changes in blood volume; the physiological changes associated with the redistribution of blood during orthostasis and lastly the results of changing vasomotor tone.

The low pressure system by definition comprises all postarteriolar vessels including the pulmonary circulation and the heart (Gauer and Henry, 1963). At any given vasomotor tone, intrathoracic pressures and filling, are determined by the blood volume and its distribution between the intra- and extrathoracic vasculature. The low pressure system is highly compliant. It holds about 85 % of the total blood volume and large fluctuations in blood volume give

rise to but small changes in the central venous pressure. For instance, in supine healthy men, central venous pressure varied by only 7 cm of water for a blood volume change of 1000 ml (Gauer, Henry, Sieker, Edelberg, 1956). Since, however, the intra-/extrathoracic compliance ratio is normally unity, half of an induced blood loss will originate from the intrathoracic and the other half from the extrathoracic vasculature. Hence a change in central venous pressure of 7 cm H_2O for a change in blood volume of 1000 ml, does in fact represent a change of 500 ml in the intrathoracic blood volume (Echt et al., 1974, Dehnen-Seipel et al., 1976).

In every-day-life central blood volume varies by considerable amounts with changing body position in the earth's gravitational field. In the upright position man pools about 500 ml in his legs up to the groin due to the increase in hydrostatic pressure (Henry et al., 1955) with 78 % of this volume coming from the intrathoracic vasculature (Sjöstrand, 1953, Gauer and Thron, 1962).
The leg congestion test used in this study mimicked these orthostatic changes by pooling about 500 ml of blood in the lower limbs. This resulted in a fall in the central venous pressure of 3.5 cm and a decrease in the blood content in both the intrathoracic and splanchnic regions. With the foregoing in mind therefore, leg congestion must have effectively depleted the intrathoracic and splanchnic vasculature by about 250 ml blood respectively.

Finally, intrathoracic pressure and filling are also under the influence of vasomotor tone. Anaesthetized dogs with normal blood volumes and vasomotor tone have a mean circulatory filling pressure of 7 mmHg, minimally 4.5 mmHg when all neural influences are blocked as in the case with total spinal anaesthesia and maximally 18 mmHg during the maximum action of adrenaline (Guyton, 1954). These observations demonstrate the potential capability of the organism to control its circulatory filling pressure by changing vasomotor tone, but at the same time it should be noted that any significant increase in venomotor tonus will only be a consequence of imminant circulatory collapse. This has been shown in healthy men in whom the pulmonary circulation was depleted by applying suction to the lower trunk. With progressive suction, the central venous pressure decreased as long as the arterial pressure was maintained by cardiac acceleration and an increase in the systemic peripheral resistance. When vasovagal syncope occurred however, the central venous pressure suddenly increased as a result of the strong venomotor effort (Murray et al., 1968, Shepherd, 1980). Venomotor tone is obviously important to the adjustment of cardiac filling pressures by controlling blood volume distribution. This however, does not seem to be the mechanism for reflex control of cardiac filling as long as an adequate systemic arterial pressure is maintained.

4.3 Blood volume distribution during peridural anaesthesia

If one assumes that a change in radioactivity is a reflection of a change in blood content within a given region, the present study then supports previous observations in which pooling within the denervated region and vasoconstriction in the innervated regions was demonstrated (de Marées, 1975, Castenfors et al., 1975). Not previously demonstrated however, is the reduction in cardiac filling in all, and a reduction of splanchnic filling in most of the subjects. It should be emphasized that scintillography yields information only about the relative distribution of the blood. Still, using these underlying measurements in conjunction with plethysmography, a reasonable estimate of the actual volume shifts can be determined. For example, changes in the intrathoracic and abdominal counting rates are quantitatively duplicated by the leg congestion test such that intrathoracic and abdominal blood volume is reduced by 250 ml respectively. About half of this volume is pooled in the denervated musculature. Calf volume, which can be considered representative of a muscle mass, increased by about 1 ml per 100 ml of tissue. In man, the total muscle mass amounts to 40 % of body weight. If one assumes that two thirds of the total muscle mass is denervated, the pooling effect amounts to some 200 ml in the denervated muscle region alone. If this figure is compared with the leg congestion test one must assume that a similar volume is accomodated in the denervated skin. From

a practical point of view it is of interest to note that the small fall in central venous pressure of only 1.25 cm of water is a poor indicator of the actual change in intrathoracic filling, possibly in part due to the altered respiratory pattern which accompanies PDA.

Nevertheless, the PDA-induced decrease in cardiac filling is small if compared for example with the effects of orthostasis and as such does not constitute a hazardous situation. This is also evidenced by the stability of the systemic arterial pressure in most subjects. It does seem clear from these observations however, that during PDA, cardiovascular stability is somehow linked with the behaviour of the splanchnic vasculature. A surprising finding was the PDA-evoked decrease in splanchnic filling which in all likelihood counteracted pooling of the blood in the denervated musculature. This in turn is likely to have favoured central blood volume. In fact, cardiac filling and systemic arterial pressure fell strongest in the two subjects in whom splanchnic filling did not decrease, but increased during PDA. The occurance of vasovagal syncope in one of the subjects may be coincidental but it may also have resulted from a failure of the splanchnic circulation to discharge some of its blood volume into the central circulation, a consequence of which being that cardiac filling was compromised and the cardiac output fell sufficiently to prevent an adequate systemic arterial pressure from being maintained. The effectiveness of the splanchnic vasculature as a

potential source for blood in case of blood loss has been shown in human volunteers. After a hemorrhage of 1 l of blood, which elicited early signs of imminant fainting in all subjects, splanchnic blood volume was reduced by 0.6 l but central blood volume by only 0.2 l (Price et al., 1966).

A paucity of reports are available on the nervous control of splanchnic filling. Splanchnic flow resistance seems to be regulated via sympathetic influences. In man, splanchnic flow resistance increases strongly with lower body suction in parallel with depletion of the central blood volume (Johnson et al., 1974) and, at least in hypertensive subjects, this effect is abolished by surgical sympathectomy (Wilkins, 1951). Since PDA in the present experiments certainly eliminated sympathetic neural and also adrenal influences, the decrease in splanchnic filling is difficult to reconcile with the sympathetic block which in other tissues like muscle and skin, for example, acts in the opposite direction. Whether this implies that an efferent parasympathetic link to the vasculature exists is at present unclear. It is attractive to consider such a mechanism since the only subject who actually fainted had clear signs of vagal activation.

It seems plausible therefore to state that sympathetic block associated with PDA does augment primarily filling in the denervated musculature and skin at the expense of cardiac filling. This is normally counteracted by a com-

pensatory constriction of capacitance vessels in the remaining innervated muscle and skin areas, by a reflex increase in sympathetic tone, and by constriction of the capacitance vessels in the splanchnic area, the mechanism of which is presently unknown. Circulatory collapse seems to ensue when for what ever reason, the venoconstrictor response by the splanchnic circulation fails.

4.4 The action of vasoactive drugs during peridural anaesthesia

Arterial hypotension sufficient to necessitate treatment occurs in only 5 % of all major conduction anaesthetics (Tolksdorf, 1983). It is thus an uncommon, although when untreated, potentially hazardous complication. For prophylaxis, it is common practice to provide intravenous infusions of crystalloids or oncotic fluids before and during the course of anaesthesia (Jenkins et al., 1975). Although such fluids certainly increase cardiac filling and thereby cardiac output, they also lower blood viscosity, one of the main determinants of flow resistance and thus tend to foster the development of arterial hypotension. In addition, the redistribution of the enlarged blood volume back to the intrathoracic vasculature upon resumption of normal sympathetic tonus may lead to pulmonary congestion and possibly also oedema.

A more rational approach would seem to be the judicious use of vasoconstrictor agents that counteract the primary disturbance namely, the loss of vasomotor tone. Bromage

drew attention to this and advocated a continuous infusion of noradrenaline to reestablish the normal endogenous catecholamine output (Cohen et al., 1959, Bromage, 1960). Noradrenaline however, normalizes peripheral flow resistance but abolishes the flow increase in the denervated region which is a desirable side effect of PDA, particularly when carried out for vascular surgery. Other studies in human subjects with upper thoracic and total peridural block have indicated that noradrenaline by itself does not reverse the circulatory changes which occur during peridural block (McLean et al., 1967). These authors noted that without any ß-vasodilator influence of epinephrine, the predominant effect is vasoconstrictive, enhancing cardiac performance only by raising the systemic vascular resistance, whereas when isoproterenol almost a pure ß-stimulator, was used, a significant improvement in cardiac index with diminished systemic resistance was achieved. It is interesting that these studies tended to focus on cardiac work and generalized vasoconstriction rather than on selectively looking at venous filling. The present study was prompted by the foregoing dilemma. Dihydroergotamine and etilefrinehydrochloride, both of which constrict preferentially the capacitance but have only minimal effects on resistance vessels (Mellander and Nordenfelt, 1970, Mellander, 1966) appeared to be a promising choice of drugs to counteract the altered blood

volume distribution during PDA because both agents have different sites of action. In healthy man with intact sympathetic innervation, DHE mobilizes blood selectively from muscle regions, while E has an effect primarily on the splanchnic vasculature. In combination, both agents increase central venous pressure and cardiac filling in an additive fashion (Arndt et al., 1984). The present observations confirm that this effect holds true also during the course of PDA.

Some minor differences between the two studies are more of a theoretical than practical importance. In combination with PDA, DHE increased thoracic filling but unlike the previous study, also filling of the splanchnic region. E, which had no effect on the lower limbs in the previous study, caused a slight reduction in the filling volume under PDA. It would appear therefore that vasomotor tone to some extent determines the quality of drug action. From a practical aspect it is important to note that dihydroergotamine displaced blood from the muscle regions to both the thorax and abdomen and that E in turn, displaced blood preferentially from the splanchnic region in favour of intrathoracic filling.

The blood mobilizing action of DHE is indeed strong. Calf volume decreased by a total of 2 ml per 100 ml tissue, that is twice the pooling effect induced by PDA. Since DHE constricted vessels in both innervated and denervated muscle beds it would have been responsible for displacing about

500 to 600 ml of blood from the total musculature, a result that would be divided between the thoracic and splanchnic vasculature. The increase in central venous pressure of 3.5 cm water is strongly suggestive that 250 ml of blood was taken up by the central vascular compartment. The success with which E reduced the splanchnic blood content can be appreciated when this effect is compared with the leg congestion test (see fig. 2). As E was equieffective in terms of the change in counting rates, the estimate that 250 ml of blood was displaced from the splanchnic region can be readily assumed. This is reflected by a further increase in the central venous pressure of 3.5 cm of water.The study dramatises the fact that DHE and E mobilized blood from different sources and together they increased central venous pressure and intrathoracic filling in an additive fashion. From a clinical perspective, their combined effects are equivalent to the transfusion of 1 l of blood (Gauer et al., 1965). Moreover, the preferential action of E in the splanchnic circulation merits particular attention. If the circulatory collapse which is occasionally associated with peridural anaesthesia does indeed relate to a dilatation of the splanchnic circulation then E would appear to be the drug of choice to counteract or prevent this destabilizing complication.

4.5 Effects of DHE and E on peripheral blood flow during PDA

The foregoing changes in the distribution of blood reflect

a primary response by the capacitance vessels since they contain the bulk of the blood volume. The effects of DHE on the capacitance versus resistance vessels are clearly dissociated during PDA in a similar manner to its actions on vessels with an intact innervation (Mellander and Nordenfelt, 1970).

DHE which greatly reduced calf volume had hardly any effect on calf blood flow, i.e. it did not reduce the PDA induced flow increase. At first sight, these results seem to conflict with a previous report showing a decrease in flow in the denervated calf region (Castenfors et al., 1975). Although in this study blood flow was twice the control values during the combined action of PDA and DHE not much significance can be given to this report for two reasons. Firstly, the dose of 0.8-1.0 mg/kg was twice that used in the present study, and secondly, epinephrine, which was added to the local anaesthetic, is very likely to have affected their measurements (Bonica et al., 1971).

The effects of E are less clearly separated from those arising from the possible return of sympathetic function as the block receded during the latter part of this experimental phase. During the infusion, calf blood flow did decrease but remained half of the maximum flow rate which occurred during PDA. A conservative conclusion would be to state that even when E acts in combination with DHE, the desirable effects of PDA are preserved and

muscle blood flow within the denervated region is still higher than before the block is induced.

4.6 Concluding remarks

The loss of neural and adrenal influences that are associated with PDA alter the distribution of blood at the expense of cardiac filling. The principle event seems to be the blood pooling in the denervated muscle and skin regions which accomodated about 600 ml of blood in healthy subjects with a sensory block up to T4/5. Since the intrathoracic vasculature was depleted by only 250 ml however, blood must have been expelled from other areas in favour of the pulmonary circulation. The innervated upper limbs is one source, the other the splanchnic vasculature where blood content was reduced by approximately 250 ml during PDA. The last is the most surprising observation of ours because, in other tissues like skeletal muscle and skin, a loss of vasomotor tone elicits vasodilation, but not vasoconstriction. Splanchnic vasoconstriction seems to ameliorate a PDA induced depletion of the central circulation whereas in cases of splanchnic vasodilation cardiac filling is jeopardized which may result in circulatory collapse.

The PDA induced depletion of the intrathoracic filling could be reversed by DHE and E. DHE mobilized blood preferentially from the skeletal musculature, but E from the splanchnic bed in favour of the pulmonary circulation.

E merits particular attention. If the circulatory collapse which is occasionally associated with PDA does indeed relate to a dilatation of the splanchnic circulation then E would appear to be the drug of choice for the prophylaxis and treatment of this destabilizing complication.

5. Summary

The experiments were carried out to determine the influences of peridural anaesthesia (PDA) and vasoactive drugs on the distribution of blood in healthy men. This was made possible by observing the distribution of technicium labelled erythrocytes by whole-body scintillography in conjunction with plethysmography in the lower limbs.

Eight healthy men volunteered for these experiments. They were studied in the horizontal decubitus position at a room temperature of 27°C. Erythrocytes were labelled with technicium (^{99m}Tc=5 mCi=5x37MBq). PDA was induced via a catheter inserted at L2/L3.

The effects of PDA up to T4/5 (20 ml lidocaine 2 %) were observed on the blood distribution (whole body scintillography), blood volume and also flow in the lower limbs (plethysmography), central venous pressure (catheter in the upper caval vein), heart rate and also arterial blood pressure (sphygmomanometry).

During PDA, blood content increased only in the denervated limbs (+9.9±4.2 %) with calf volume increasing by 1 ml per 100 ml tissue. In all other regions, blood content decreased in the thorax (-9.8±1.5 %) the innervated upper limbs (-9.9±2.3 %) and curiously also in the splanchnic vasculature (-3.6±2.0 %). Interesting, in two subjects splanchnic blood volume increased after an early fall. This was associated with the greatest decrease in intrapulmonary filling, and arterial

pressure. The vasovagal syncope which occurred in one subject is very suggestive that the lack of splanchnic vasoconstriction may jeopardize adequate cardiac filling thus leading to circulatory collapse.

Depletion of the pulmonary circulation associated with PDA could be duplicated by the leg congestion test during which about 600 ml of blood were sequestered in both legs.

DHE (7.5 mg/kg intravenously) reversed the PDA-induced effects. It decreased the blood content in the denervated legs (-8±2.7%) and in the innervated arms (-18±2.5%) in favour of both the intrathoracic (+4.2±1.2%) and splanchnic vasculature (+3.8±1.4%). Calf volume decreased by 1.67 ml/100 ml tissue.

E (6 µg/kg/min) decreased the blood content preferentially in the splanchnic vasculature (-5.05±5%) in favour of the intrathoracic circulation (+1.9±1.6%).

In combination, both agents increased central venous pressure (+6±0.8 cm water) and intrathoracic filling (+6.5±1.6%) in an additive fashion, an effect which is equivalent to transfusion of approximately 1 l blood.

Calf blood flow, that was doubled during PDA (from 1.9 to 4.1 ml/100 ml tissue/min) was not affected by DHE and remained during the infusion of E well above the control values.

The loss of vasomotor tone and also of adrenal influences that are associated with major conduction anaesthesia elicit a blood volume redistribution at the expense of cardiac filling

the principle event being the pooling of blood in the denervated muscle and skin areas. This is normally counteracted by a vasoconstriction in the innervated muscle and skin regions and most surprisingly in most subjects also with a constriction of the splanchnic vasculature from where blood is being shifted into the central compartment. The occurrance of circulatory collapse during PDA appears to be somehow linked with the behaviour of the splanchnic circulation. Splanchnic vasoconstriction seems to ameliorate a PDA-induced depletion of the central circulation whereas in case of splanchnic vasodilation cardiac filling is jeopardized which may result in circulatory collapse.
The PDA-induced depletion of the intrathoracic circulation can be effectively counteracted by DHE which mobilizes blood preferentially from the skeletal musculature and particularly by E which expels blood selectively from the splanchnic circulation.

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Lebenslauf

Am 3. Juni 1931 wurde ich als Sohn des Arztes und Professors der Physiologie und Pharmakologie, Cedric Stanton-Hicks und seiner Frau Florence in Adelaide, Australien, geboren. Ab 1936 besuchte ich das Sankt Peters College, Adelaide. Ich verließ die Schule 1950 um eine Pilotenausbildung zu machen. 1952 machte ich mein Abitur und studierte von 1953 bis 1960 in Melbourne/Australien Medizin.
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